Pathway to Prevention of Nosocomial Clostridium difficile Infection

Ellie J. C. Goldstein,1 Stuart Johnson,2 Pierre-Jean Maziade,3 Lynne V. McFarland,4 William Trick,5 Linda Dresser,6 Mathieu Millette,7 Hadi Mazloum,7 and Donald E. Low8,a

1RM Alden Research Laboratory and the David Geffen School of Medicine at UCLA, Los Angeles, California; 2Hines VA Hospital and Loyola University Medical Center, Chicago, Illinois; 3Centre Hospitalier Pierre-Le Gardeur, Terrebonne, Quebec, Canada; 4Department of Medicinal Chemistry, University of Washington, Seattle; 5Collaborative Research Unit, Chicago, Illinois; 6Leslie Dan Faculty of Pharmacy, University of Toronto, Ontario, 7Bio-K Plus International Inc, Laval, Quebec, and 8Mount Sinai Hospital, University of Toronto, Ontario, Canada

Background. To address the significant morbidity and mortality rates associated with nosocomial Clostridium difficile–associated diarrhea (CDAD), a series of recommendations and a pathway to prevention were developed.

Methods. An expert panel of infectious disease (ID) specialists participated in a modified Delphi process with specific objectives: (1) conduct a review for CDAD and prevention; (2) develop statements based upon panel members’ opinions; (3) hold a panel meeting during the 2012 IDWeek; and (4) review the final recommendations and prevention pathway prior to submission for publication.

Results. The panel voted on (1) antibiotic stewardship (7 of 8 panelists); (2) reduction of other potentially modifiable risk factors (variable); (3) utilization of specific probiotics to prevent C. difficile overgrowth (8/8); (4) staff education regarding CDAD preventive measures (8/8); (5) appropriate hand hygiene for everyone (7/8); (6) environmental cleaning (8/8); (7) medical equipment disinfection (7/8); (8) early detection of CDAD in symptomatic patients (7/8); (9) usage of protective clothing/gloves (8/8); (10) proper measures during outbreak (8/8); and (11) surveillance to monitor efficacy data of preventive measures (8/8).

Conclusions. The panel members agreed with 11 of 17 recommendations presented. The additional recommendations by the panel were proton pump inhibitor use as a risk factor and the use of adjunctive therapy with specific probiotic, as it was approved by Health Canada for the risk reduction of CDAD in hospitalized patients.

Keywords. Clostridium difficile; prevention; CDI; probiotic.

Hospital-acquired infections are a growing issue. Administration of antibiotics disrupts natural intestinal microbiota, paving the way for anaerobic gram-positive bacteria overgrowth such as Clostridium difficile, as well as the production of its toxins A and B, which can induce inflammation of the bowel and diarrhea [1]. Clostridium difficile–associated diarrhea (CDAD) ranges from mild to severe and, in some cases, may require surgical intervention. In severe cases, nosocomial CDAD can result in mortality [2, 3]. In the United States, approximately 500 000 persons per year suffer from CDAD [4], with an estimated death toll of 793 in 1999, 7483 in 2008, and 7285 in 2009 [5]. A total of 3934 CDAD cases were reported in Quebec hospitals from 2010 to 2011; 3661 cases were more closely monitored, of which 619 resulted in death [6]. CDAD also has a substantial economic impact. In 2006, in a German tertiary care university hospital, the average additional cost for treating 1 CDAD patient was approximately €7147 (US$9561) [7]. This study also revealed that the hospital stay for patients developing CDAD (median, 27 days; n = 45) was longer than for their matched controls (median, 20 days, n = 135; P = .006) [7]. Fansi et al determined that the average cost of a CDAD case is approximately €7147 (US$9561) [7]. This study also revealed that the hospital stay for patients developing CDAD (median, 27 days; n = 45) was longer than for their matched controls (median, 20 days, n = 135; P = .006) [7]. Fansi et al determined that the average cost of a CDAD case is approximately US$9115 (assuming an average 6.4-day hospital stay per infected patient) [8]. Other published studies identify a similar cost range ($10 000–$15 000) [9–11]. Annual expenditures in the...
United States to manage CDAD are $3.2 billion per year (data collected from 1999 to 2003) [11].

The spore form of C. difficile is resistant to antibiotics; it spreads easily and resists regular cleaning procedures [3]. Prevention procedures were established in 2008 by the European Centre for Disease Prevention (ECDP) [3] and by the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) in 2010 [12].

The ECDP [3] proposed 9 recommendations: early detection of CDAD, surveillance for CDAD cases, staff education on infection control, proper deployment of isolation precautions, appropriate hand hygiene, usage of protective clothing, cleaning of surroundings and medical equipment, good antibiotic stewardship, and proper measures during outbreaks [1, 2]. These recommendations are in line with those made by the SHEA/IDSA group: hand hygiene, contact precautions, adequate hospital facilities, prevention of C. difficile carriage by healthcare workers, and antimicrobial use restriction.

SHEA/IDSA do not recommend probiotic usage for adjunctive therapy with antibiotics. The Yale University Workshops on the “recommendations for probiotic use in humans” of 2011 and 2014 [13, 14] gave grades of B/C for the use of Saccharomyces boulardii and Lactobacillus GG in prevention of CDAD and for CDAD recurrence. However, Health Canada recently approved a particular combination of probiotic bacteria for the risk reduction of CDAD in hospitalized patients: Bio-K+ contains 50 billion colony-forming units (CFUs) of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R. Review of the available literature suggests that primary prevention of CDAD with specific probiotic agents may be achievable [15-18].

Clinical trials have demonstrated that the administration of a probiotic formula containing L. acidophilus CL1285 and L. casei LBC80R reduces incidents of nosocomial CDAD and lowers healthcare costs [8, 19-21]. In addition, other probiotic products, such as those containing Bifidobacterium, Lactobacillus, S. boulardii, and Streptococcus thermophilus, have also been studied for CDAD prevention [22]. Safdar et al [23] had 0 cases of CDAD (n = 3) in their treatment group using L. acidophilus (strain not reported) compared with 1 case in the control group (n = 4), but the results were not statistically significant (P = .15). Another study using a mixture of L. casei DN-114001, Lactobacillus delbrueckii subspecies bulgaricus, and S. thermophilus had 0 of 56 cases of CDAD in the treatment group and 9 of 53 (17%) cases of CDAD in the control group (n = 53; P = .001) [24]. A meta-analysis of 4 studies using S. boulardii suggests a lower CDAD rate (risk ratio, 0.70; 95% confidence interval [CI], 0.29-1.69) [18]. However, Pozzoni et al found no significant difference with S. boulardii in their randomized controlled trial (RCT) for CDAD (odds ratio, 1.40; 95% CI, 0.23-8.55) in an elderly population [25].

With these results in hand, combined with a few recommendations pertaining to probiotics in C. difficile prevention, a Delphi panel procedure was established to explore preventive measures for inpatients.

ROLE OF THE PANEL

The expert panel developed key statements regarding CDAD prevention. It consisted of 8 internationally recognized infectious disease specialists, pharmacists, and scientists from the United States and Canada, all dedicated to medical microbiology. The group included Ellie J. C. Goldstein (MD; chairperson), Donald E. Low (MD; co-chair), Brian Currie (MD), Curtis Donskey (MD), Stuart Johnson (MD), Pierre-Jean Mazia de (MD), Linda Dresser (PharmD), and Lynne V. McFarland (PhD). The healthcare professionals (HCPs) identified above manage patients with CDAD on a regular basis.

PROCEDURE USING THE MODIFIED DELPHI METHOD

1. A literature review was carried out using online databases.
2. From this literature search, a series of proposed recommendations regarding CDAD prevention was developed by all of the authors.
3. A meeting was held, and these recommendations (along with relevant support from the literature) were reviewed by the expert panel in accordance with the modified Delphi method. The meeting chair, Dr Ellie Goldstein, guided the meeting.
4. Panel members were asked to provide their opinions from a clinical perspective and were given the opportunity to adapt the statements. Following this, the panel voted on each motherhood statement.
5. Following all motherhood statements, a pathway to the prevention of CDAD was developed and recommended.

LITERATURE REVIEW

A literature review was carried out on PubMed, OvidSP, and Google Scholar for nosocomial CDAD recommendations for preventing and treating this disease. Furthermore, a secondary analysis of related citations and references was conducted. The following keywords were used: Clostridium difficile infection and prevention, CDAD, CDI, nosocomial, probiotic, Lactobacillus, Bifidobacterium, Saccharomyces, staff, diagnosis, surveillance, education, isolation, precaution, hand hygiene, protective, clothing, environmental cleaning, equipment cleaning, antibiotic stewardship, outbreak, and specific measure. The search was limited to the time frame between 1 January 2008 and 15 June 2012. For this review, we analyzed the articles identified in our original
search, as well as articles cited in the original review articles. With respect to medical treatment, we based our review on guideline articles, systematic reviews, and available RCTs.

**Results of the Literature Search**
The literature search produced a total of 6697 articles, including reviews and meta-analyses. Two authors (M. M. and H. M.) reviewed the publications and selected those pertaining to CDAD prevention.

The search was divided into 11 categories, in line with the recommendations in the review articles dealing with the prevention of nosocomial CDAD. The categories are the following: antibiotic stewardship, potentially modifiable risk factors, utilization of specific probiotic to prevent *C. difficile* overgrowth, staff education regarding CDAD preventive measures, appropriate hand hygiene for everyone, environmental cleaning, medical equipment disinfection, early detection of CDAD in symptomatic patients, usage of protective clothing/gloves, proper measures during outbreak, and surveillance to monitor efficacy of preventive measures.

Key points identified by the search were as follows:

- Infection will most likely occur when the patient is receiving concomitant antimicrobial therapy, especially with broad-spectrum antibiotics such as cephalosporins, penicillins, amoxicillin, clindamycin, and fluoroquinolones [1, 3].
- Utilization of antibiotics causes the alteration of a substantial part of the intestinal microbiota—its richness, diversity, and evenness—facilitating bacterial growth, toxin production, and sporulation of *C. difficile*.
- Release of spores is achieved when the patient excretes them during CDAD episodes or as a carrier.
- Spores easily survive because they cannot be destroyed by standard alcohol-based hand disinfectants nor by most other environmental cleansing agents [3]. This heightens the risk of transmission, so early prevention of the disease is critical.
- Literature shows that the utilization of some specific probiotic products could help reduce the risk of CDAD. In fact, it is thought that these probiotics repopulate the intestinal flora, thus preventing *C. difficile* from reaching overwhelming numbers [19–21].

**STATEMENTS FOR PANEL DISCUSSION**

The preventive measures were divided into 3 categories: (1) reduction of host susceptibility; (2) prevention of *C. difficile* exposure in susceptible patients; and (3) monitoring of the efficacy of preventive measures.

Primary prevention refers to preventing *C. difficile* infection in a patient, caused either by antibiotics or another risk factor. If a first infection occurred in a hospital, that triggers the second stage of prevention to thwart the threat of a potential epidemic. Preventing exposure among susceptible patients was the main priority, and measures were monitored to track their effectiveness.

Furthermore, each of the prevention measures was graded according to the 2010 SHEA/IDSA grading system [26]. The present article is an update on the prevention measures grading system made by Cohen et al [26]. The system confers 2 grades (1 or 11) for every measure taken in the following 2 categories: strength of recommendation and quality of evidence (Table 1). This article addresses quality of evidence, and grades the preventive measures. A search on PubMed was performed in an attempt to update the quality of evidence previously suggested by Cohen et al [26].

The following statements had at least 1 RCT, conferring a grade I for quality of evidence:

- Utilization of specific probiotics to prevent *C. difficile* overgrowth.
- All HCPs working with CDAD patients should wear gloves or protective clothing.

Grade II quality of evidence was accorded to the following statements for having 1 well-designed clinical trial or case-control study:

- Antibiotic stewardship
- Proton pump inhibitors (PPIs)
- Statins
- Hyponutrition
- Appropriate hand hygiene for everyone
- Regular cleaning with sporicidal agents should be performed in room where patients had CDAD following the Centers for Medicare and Medicaid Services recommendations

<table>
<thead>
<tr>
<th>Category and Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
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<tr>
<td>A</td>
<td>Good evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for or against use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from at least 1 properly randomized controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from &gt;1 center), from multiple time series, or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experiences, descriptive studies, or reports of expert committees</td>
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**Table 1. Definition of the Strength of Recommendations and the Quality of the Evidence Supporting Them [26]**
Medical equipment disinfection

Rapid and sensitive diagnostics testing and isolation of C. difficile–infected patients

All CDAD preventive measures should be executed when an outbreak occurs

Surveillance data to monitor efficacy of preventive measures

The panel voted on each statement, which was graded on a scale of 1–8, representing the number of members of the panel that agreed with the measure. Therefore, 0/8 means that no members agreed with the statement proposed, and 8/8 means that every member of the panel agreed with the recommendation. Results of the vote are summarized in Table 2.

1. Minimize Host Susceptibility

Antibiotic Stewardship: A-II

Proposed statement 1a (7/8): Physicians should avoid unnecessary antibiotics, use appropriate duration of therapy, and consider the associated risk of an antimicrobial for causing CDAD and select antibiotics using a 2-step situational analysis.

No RCT was conducted to support this statement. However, good clinical trials and case studies have clearly demonstrated the utility of antibiotic stewardship to prevent CDAD [32–34]. Antibiotic stewardship is a measure that strikes at the root of the problem as it could prevent CDAD before it happens. When the physician must choose an empiric antibiotic, ideally it should not be a drug with a high propensity to lead to the outgrowth of C. difficile in the host intestine. The decision process for choosing an antibiotic should involve a 2-step situational analysis.

- Clinicians should consider the level of risk that an antibiotic poses to the patient, which in the case of CDAD can be low or high.
- Second, the clinician should consider how long the patient will be taking antibiotics.
- Finally, broad-spectrum antibiotics with a high risk of causing CDAD should be avoided if possible (Table 3).

Reduce Other Potentially Modifiable Risk Factors

Proposed statement 1b: Other preventive measures should be considered in line with the situation. Medications taken by the patients should be taken into account.

Medication Influencing CDAD Incidence

Proton Pump Inhibitors: B-II (8/8)

It has been reported that the use of PPIs leads to higher rates of CDAD [38]. PPIs cause a reduction in gastric acid production, but also potentially disrupt the intestinal microbiota, allowing C. difficile to overgrow. Gastric acid has an important role in eliminating the ingested non-spore-forming pathogens, but this role in eliminating C. difficile is speculative [38] (91).

A meta-analysis including 23 studies on 288 620 patients undergoing PPI treatment showed a 65% increase of CDAD cases in patients who were taking PPIs (risk ratio [RR], 1.69; 95% confidence interval [CI], 1.40–1.97; P < .001) [38]. This meta-analysis did not include an RCT, which is why this preventive measure is graded B-II, even with the numerous studies demonstrating the relation between PPI intake and CDAD incidence.

Moreover, recurrence of CDAD may be associated with PPI use, as suggested in an article reporting that 95% of the 20

### Table 2. Summary of Strength of Recommendation, Quality of Evidence, and Panel Vote Results for Each Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation and Quality of Evidence</th>
<th>Panel Vote Results</th>
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<tbody>
<tr>
<td>Antibiotic stewardship</td>
<td>A-II</td>
<td>7/8</td>
</tr>
<tr>
<td>Reduce other potentially modifiable risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Proton pump inhibitors</td>
<td>B-II</td>
<td>8/8</td>
</tr>
<tr>
<td>(b) Statins</td>
<td>C-II</td>
<td>0/8</td>
</tr>
<tr>
<td>(c) Opioid analgesics</td>
<td>C-III</td>
<td>NSD</td>
</tr>
<tr>
<td>(d) Corticosteroids</td>
<td>C-III</td>
<td>0/8</td>
</tr>
<tr>
<td>(e) Chemotherapy</td>
<td>C-III</td>
<td>0/8</td>
</tr>
<tr>
<td>(f) Hyponutrition and elemental diets</td>
<td>C-III</td>
<td>NSD</td>
</tr>
<tr>
<td>(g) Tube feeding and catheter</td>
<td>C-III</td>
<td>NSD</td>
</tr>
<tr>
<td>Utilization of specific probiotic to prevent C. difficile overgrowth</td>
<td>B-I</td>
<td>8/8</td>
</tr>
<tr>
<td>Staff education regarding CDAD preventive measures</td>
<td>B-III</td>
<td>8/8</td>
</tr>
<tr>
<td>Appropriate hand hygiene for everyone</td>
<td>A-II</td>
<td>7/8</td>
</tr>
<tr>
<td>Environmental cleaning</td>
<td>B-II</td>
<td>8/8</td>
</tr>
<tr>
<td>Medical equipment disinfection</td>
<td>B-II</td>
<td>7/8</td>
</tr>
<tr>
<td>Early detection of CDAD in symptomatic patients</td>
<td>A-II</td>
<td>7/8</td>
</tr>
<tr>
<td>Usage of protective clothing/gloves</td>
<td>A-I</td>
<td>8/8</td>
</tr>
<tr>
<td>Proper measures during outbreak</td>
<td>A-II</td>
<td>8/8</td>
</tr>
<tr>
<td>Surveillance to monitor efficacy of preventive measures</td>
<td>A-II</td>
<td>8/8</td>
</tr>
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Abbreviations: CDAD, Clostridium difficile–associated diarrhea; NSD, no sufficient data to vote.

### Table 3. Antibiotic Stewardship

<table>
<thead>
<tr>
<th>High-Risk Antibiotics [2, 27–31]</th>
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<tr>
<td>• Fluoroquinolones</td>
</tr>
<tr>
<td>• Cephalosporins</td>
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<tr>
<td>• Clindamycin</td>
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</table>

* High risk of CDAD-associated antibiotics.
patients in the relapse group were receiving long-term PPI therapy ($P = .029$), vs 74% of the 104 nonrelapsing patients [39].

**Statins (Blood Cholesterol-Lowering Drugs—The 3-hydroxy-3-methylglutaryl-coenzyme [HMG-CoA] Reductase Inhibitor): C-II (0/8, Weak Evidence)**

A recent study demonstrated that statins can decrease occurrence of CDAD. The findings showed that the pleiotropic effects of statins can protect patients from CDAD. Users of statins were 22% less likely to develop CDAD. The difference between the various statins used in the study was minimal. However, the authors also found that resin (blood cholesterol-lowering drug, increased occurrences of CDAD [40]. Results reported by McGuire et al [41] demonstrated that CDAD was higher among patients taking statins. Their hypothesis is that the pleiotropic effect of statins acts on the Rho pathway, just like toxins A and B of *C. difficile*, increasing CDAD. Therefore, more studies are needed to confirm the role of statins in this disease.

Because the literature is limited and the available results are contradictory, the panel of experts could not offer an opinion on the role of statins in CDAD prevention. Statins are an important medication used to reduce blood cholesterol level and prevent cardiovascular events. Hence, the risk-benefit analysis suggests continuation of statin therapy.

**Opioid Analgesics, Corticosteroids, and Chemotherapy in CDAD Incidence**

- **Opioid analgesics: C-III (panel did not vote because there is not enough evidence available)**
- **Corticosteroids: C-III (0/8)**
- **Chemotherapy: C-III (0/8)**

Opioids are potent analgesics used to control pain, allowing a higher tolerance level. Occurrence of CDAD could increase with moderate to high opioid administration. In fact, the delayed passage of intestinal content caused by these antimitotic agents allows closer contact of *C. difficile* with the mucosa, increasing significantly the chances of infection [42].

Dhalla et al have shown that corticosteroid use increases the risk of CDAD [43]. Schneeweiss et al [44] have evaluated 10,622 patients with inflammatory bowel disease. The outcome ranged from a 1.5- to 3-fold increase in CDAD rates among patients taking corticosteroids [43, 44].

Five mechanisms to explain a correlation between chemotherapy-associated *C. difficile* colitis and CDIs have been hypothesized [36]:

1. Alteration of the intestinal microbiota
2. Nosocomial infection with *C. difficile* prior to chemotherapy treatment
3. Increased risk of CDAD such as antibiotic usage, hospitalization, and age (65 and older)

4. Increased colonic mucosa damage
5. Reduction in repair capacities of the mucosal epithelium

Antineoplastic chemotherapy causes mitotic arrest in the human and animal gastrointestinal (GI) tract. Not all chemotherapeutic agents have the same effect. Table 4 provides an overview of the effects caused by these drugs.

Some studies demonstrated a greater increase in CDAD incidents among patients undergoing chemotherapy. Mayumi et al [45] detected CDAD in 8 of 10 children treated with antineoplastic agents and antibiotics. Six infected children had no infection when they were admitted to the hospital. The increased rate of CDAD may have been due to the prolonged hospitalization [46]. Another study demonstrated an increase of 14.4% of CDAD among 104 chemotherapy patients [47], while Schuller et al [48] reported an increase of 13%.

Each of these drug classes (opioids, corticosteroids, and chemotherapy) has an important role in the management of specific diseases, and they are not replaceable. For this reason the panel did not vote or voted 0/8 on these statements. However, if further evidence corroborates the risk of opioids or corticosteroids, one possible recommendation might be a program to closely monitor patients taking these medications. That could lead to appropriate preventive measures and quickly detect a CDAD case if it should happen.

**Hyponutrition and Elemental Diets as a Risk Factor: C-III (Panel Did Not Vote Because There Is Insufficient Available Evidence)**

This potential risk factor was analyzed in studies where patients contracted *C. difficile* while receiving elemental diets, defined as residue-free predigested or an elementary form of nutrition delivered directly into the jejunum, and absorbed at the level of the upper small intestine [49]. This inhibits the colonic microbiota from receiving nutrients (ie, dietary fiber,
fructose oligosaccharides, and resistant starch). A lack of these nutrients leads to a reduced concentration of many good microorganisms such as butyrate-producing bacteria and bifidobacteria. Such perturbation of the microbiota can create a viable environment for *C. difficile*, and eventually an infection. Furthermore, Iizuka et al suggested that the elemental diets might cause CDAD by providing an excellent medium for the growth of *C. difficile* [50].

**Tube Feeding and Catheter: C-III (Panel Did Not Vote Because of Mixed Evidence)**

With tube feeding and catheter usage, *C. difficile* spores need not overcome microbial barriers such as skin, mucosa, and upper GI defenses [49], as nutrition is delivered directly into the stomach or duodenum. Furthermore, the tubes or catheters might be contaminated, which could also cause CDAD [51, 52]. A higher risk of CDAD was also found in patients using tube feeding devices and catheters as these same patients generally receive antibiotics intravenously peri-insertion to prevent placement infections [53]. In summary, tube feeding and catheters may increase the risk of CDAD via multiple mechanisms, but substantive evidence of an independent risk factor is lacking to date.

**Utilization of Specific Probiotic to Prevent *C. difficile* Overgrowth: B-I**

Proposed statement 1c (8/8): Consuming *L. acidophilus* CL1285 and *L. casei* LBC80R can decrease CDAD incidence. Probiotics should be added in the bundle of preventive measures to control CDAD.

Probiotics have been tested for their possible therapeutic applications in CDAD. A recent systematic review conducted in 20 randomized trials (3818 patients) showed that incidence of CDAD was reduced by 66% (pooled relative risk, 0.34; 95% CI, 0.24–0.49) with probiotic consumption [16]. Johnson et al (2012) [18] identified 11 studies in their meta-analysis for the prevention of CDAD with probiotics. The combined overall relative risk was 0.39 (95% CI, 0.19–0.79). The authors concluded that primary prevention of CDAD could be possible with specific strains. In another meta-analysis, Ritchie and Romanuk [54] reported an incidence rate of 0.60 (95% CI, 0.41–0.85) for *C. difficile*. They included 6 studies, of which only 2 had a *P* value <.05. Nevertheless, they concluded that the probiotic strain choice is the most important factor when consuming a probiotic for prevention of GI diseases. The reduction rate of CDAD reported in Avadhani and Miley [55] was 71%. These findings were collected from 8 RCTs. The authors concluded that probiotics are effective in preventing CDAD. A 41% reduction rate in CDAD was reported in McFarland [56], a meta-analysis of 6 RCTs (combined RR, 0.59; 95% CI, 0.41–0.85; *P* = .005). McFarland [56] concluded that probiotics are a promising preventive strategy for CDAD.

According to the literature, there is evidence of a correlation between the intake of Bio-K+ probiotics and the reduction of antibiotic-associated diarrhea and CDAD cases. Beausoleil et al [20] demonstrated no significant difference between the lactobacilli (*n* = 44) and placebo (*n* = 45) groups with respect to treatment-related adverse events. In a dose-response RCT, Gao et al [19] demonstrated that the daily administration of Bio-K+ capsules is safe and effective in the prevention of CDAD. In fact, CDAD incidence was 1.2% with 100 billion CFUs and 9.4% with 50 billion CFUs, compared to the placebo group, which had 23.8%. This is a 95% reduction of CDAD incidence when 100 billion CFUs of the mixture is used on patients taking antibiotics. No severe or life-threatening events related to the use of the lactobacilli preparation were reported, although there were some withdrawals associated with the occurrences of adverse events.

Recently, Maziade et al [57] reported an 8-year quasi-experimental, prospective cohort study evaluating the impact of the addition of prophylactic Bio-K+ administration to existing CDAD preventive measures in a community hospital. Overall, >31,000 patients received the probiotic intervention. Among this population, Bio-K+ was effective in reducing the CDAD rate and in reducing severe cases of CDAD. It also proved to be safe as no serious events or probiotic-related bacteremias were observed. The numbers of CDAD cases were reduced by 73% (*P* < .001) and those of severe CDAD by 76.4% (*P* < .001). Furthermore, cases of reoccurring CDAD decreased by 39% (*P* < .001). This probiotic formula was given to every hospitalized adult patient receiving antibiotics.

A pharmacoeconomic study revealed that the financial burden of CDAD can be reduced by preventing the disease. In fact, following the results observed in Gao et al [19], Farsi et al [8] assessed the medical costs resulting from probiotics vs placebo. A savings of US$1968 was associated with the intake of 1 Bio-K+ capsule and US $2661 when 2 capsules were taken. The first probiotic administration took place within 36 hours of prescribed antibiotic therapy, and daily usage of the product continued for 5 additional days following completion of antibiotic therapy. Patients took both capsules at the same time each day, at breakfast, after the antibiotic administration. Therefore, 1000 patients receiving antibiotics and a dual dose of probiotics in prophylaxis could save the healthcare system $2661 218 in treatment costs.

Also, in some in vitro studies demonstrated antimicrobial performance of *L. acidophilus* CL1285 and *L. casei* LBC80R against various strains of *C. difficile*. It was demonstrated that the cytotoxicity induced by *C. difficile* was inhibited by supernatants harvested from the strains and finished products [58]. Millette et al [59] demonstrated the GI survival of *L. acidophilus* CL1285
and *L. casei* LBC80R when encapsulated or as a fermented milk. Altogether, the in vitro data point to some mechanisms of action of this specific probiotic formula to control CDAD.

Recently, Health Canada approved a specific mixture of probiotic bacteria for the risk reduction of CDAD in hospitalized patients (Bio-K+ containing 50 billion CFUs of *L. acidophilus* CL1285 and *L. casei* LBC80R). The previous evidence is the basis for the Health Canada approval.

2. Preventing Exposure in Susceptible Patients (8/8)

**Staff Education Regarding CDAD Preventive Measures: B-III**

**Proposed statement 2a (8/8):** All healthcare institution employees, volunteers, and visitors should be educated on CDAD prevention and control measures.

Because hospital staffs are constantly exposed to patients in an environment potentially contaminated by *C. difficile*, it is critical that everyone be made aware of the measures to help control the spread of the disease. The instruction should include both general information and infection control measures. Furthermore, healthcare professionals giving home health services should familiar with the preventive measures, and convey the information to each patient and his/her family. Hospital visitors should also be made aware of preventive measures as they also can be at risk [51].

**Appropriate Hand Hygiene for Everyone: A-II**

**Proposed statement 2b (7/8):** HCPs should wash their hands with soap and water every time they remove their gloves, and when entering or leaving the room of a patient with CDAD. Patients should also wash their hands with soap and water before eating and after using the toilet.

*Clostridium difficile* spores are not completely killed by alcohol [26], which is the agent found in most hand cleansers. Therefore, in outbreak situations, thorough hand washing with soap and water is recommended to remove spores [60]. However, because no available data link an increase of CDAD rates to use of alcohol-based products, there is no recommendation of soap and water under nonoutbreak conditions [60], but soap and water should be the preferred hand-washing method during outbreaks. HCPs should wash their hands every time they remove their gloves. In addition, patients should wash their hands before eating and after using the washroom. [2, 61–64].

**Environmental Cleaning: B-II**

**Proposed statement 2c (8/8):** Rooms vacated by patients with CDAD should be regularly cleaned with sporidical agents.

Gerding *et al* [65] suggested that twice daily, frequently touched surfaces within the immediate reach of patients/residents with suspected or confirmed CDAD should be washed and disinfected. It is known that *C. difficile* spores can live for many months in patient rooms [66].

Various cleaning agents are used to wash surfaces such as light switches, door knobs, bed railings, room floors, bathrooms, electronic thermometers, blood pressure cuffs, sheets, call buttons, televisions, and tube-feeding devices [2]. The most commonly used disinfectants are quaternary ammonium compounds and phenolic acid derivatives. Unfortunately, both products cannot destroy spores. They are used because they are less corrosive and less harmful than sporidical agents such as chlorine-based disinfectants and high-concentration vaporized hydrogen peroxide [8].

Sodium hypochlorite (5.25%) is used to kill spores: Ten minutes of contact time is needed to thoroughly eliminate all spores on a surface [67]. For other products, it is important to follow the manufacturer’s directions to ensure adequate contact time [12]. Organic materials such as blood, mucus, or feces negate the efficacy of chlorine bleach. Therefore, it is important to use a cleaning product prior to a final wiping with chlorine bleach. Sporicidal agents should also be used when patients are discharged or transferred [68–70]. Also, noninfected patient rooms should be cleaned before infected patient rooms [67].

**Medical Equipment Disinfection: B-II**

**Proposed statement 2d (7/8):** Regular cleaning with sporidical agents should be done to lower the *C. difficile* spore count in hospitals.

Medical equipment can act as a spore reservoir and become the vehicle for the spread of contamination. Disinfectant cleansing should be routinely done on medical equipment such as electronic thermometers that regularly come in contact with patients as well as on other close-proximity-to-patient surfaces such as bedrails. Chlorine-based disinfectants and high-concentration vaporized hydrogen peroxide are recommended. However, inappropriate use of bleach on equipment can cause degradation. To best reduce *C. difficile* spore spreading, medical equipment should be kept in specific patient rooms, and not moved from one patient room to another [69]. If that is not possible, then they should be cleaned and disinfected before transfer [71].

Sometimes, equipment can be difficult to disinfect. Boyce *et al* demonstrated that hydrogen peroxide vapor can efficiently disinfect particularly hard-to-clean equipment [72].

**Early Detection of CDAD in Symptomatic Patients: A-II**

**Proposed statement 2e (7/8):** Implement rapid and sensitive diagnostic testing. Isolate *C. difficile*-infected and symptomatic patients.

The sooner *C. difficile* is identified as the active pathogen, the sooner measures to prevent its spread can be deployed [1,73–76]. Studies have demonstrated that the asymptomatic carriage rate is between 51% and 85% among selected prolonged-stay inpatient groups, and 6.5% in long-term, acute care settings [77,78].
Isolation of infected, symptomatic patients is the most commonly used strategy to prevent transmission of contagious diseases. It limits the contact between infected patients and noninfected patients/visitors. Isolation measures frequently curtail patient movement in hallways, and give patients a private bathroom, thus preventing contamination spread to more rooms. Data on transmission from asymptomatic C. difficile carriers are incomplete and the panel did not recommend identification and isolation of asymptomatic C. difficile carriers.

If this type of patient isolation is simply not feasible, then patient mingling, or steps to isolate an infected person within a multi-occupied room, can be considered. Ideally, patients with CDAD should be in single rooms and unnecessary transport of the patient in and out of the room should be limited [2, 63, 79, 80].

**Usage of Protective Clothing/Gloves: A-I**

Proposed statement 2f (8/8): All HCPs working with CDAD patients should wear protective clothing and gloves.

The use of gloves has been demonstrated to diminish spore carriage and CDAD infection, supporting the thesis that hands are an important vector for spreading C. difficile spores [81]. This study showed a decrease from 7.7 cases per 1000 patients to 1.5 per 1000 ($P = .015$) when vinyl gloves were worn during a particular intervention over a period of 6 months. The glove initiative consisted of informational posters, glove boxes at the patient’s bedside, plus initial and follow-up in-services.

Glove usage should not be limited to situations where there is exposure to blood, fluids, excretions, damaged skin, or open sores. They should also be worn when entering a patient’s room, where there is possibly vancomycin-resistant Enterococcus, methicillin-resistant Staphylococcus aureus, or C. difficile [82]. However, the potential benefits of washing hands with soap and water instead of using alcohol-based products tend to be nullified with an improper glove removal technique [60].

Together with gloves, a gown can be worn to limit the spread of CDAD via clothes [70, 82, 83].

**Proper Measures During Outbreak: A-II**

Proposed statement 2g (8/8): All CDAD preventive measures should be executed when an outbreak occurs.

A CDAD outbreak is defined as “two or more cases caused by the same strain related in time and place over a defined period that is based on the date of onset of the first case” [84]. All CDAD preventive measures should be deployed when an outbreak occurs.

As mentioned in proposed statement 1, the sooner the CDAD cases are confirmed, the sooner measures to prevent its spread can be deployed. That is why a low threshold and early detection measures should be priority. Isolation and cleaning must be quickly implemented to minimize the spread of C. difficile [3].

**3. Surveillance Data to Monitor Efficacy of Preventive Measures: A-II**

Proposed statement (8/8): Adopt the threshold number of cases as determined by the Ontario Ministry of Health and Long-term Care; when the threshold is reached, CDAD preventive measures are triggered.

If the number of CDI reach a critical threshold, it would trigger prespecified preventive measures in order to rapidly confine spreading of the infection [69]. Because the SHEA/IDSA did not address this topic, we chose to follow the threshold outlined by the Ontario Ministry of Health and Long-term Care [85, 86]:

- For wards/units with ≥20 beds, 3 cases of nosocomial CDAD identified on 1 ward/unit within a 7-day period or 5 cases within a 4-week period;
- For wards/units with <20 beds, 2 cases of nosocomial CDAD identified on 1 ward/unit within a 7-day period or 4 cases within a 4-week period;
- Hospitals that have a baseline CDAD rate for 2 months that is at or above the 80th percentile for comparator hospitals; or
- Hospitals that have a facility rate that is ≥2 standard deviations above their baseline.

**PROPOSED PATHWAY**

Figure 1 is a pathway to detect the most vulnerable population to CDAD. The deployment of standard preventive measures depends on antibiotic usage or not. The second criterion is age-related, as probiotics should be given to 18 years and older patients, since no data is available for younger population. For patients younger than 18 years old, standard preventive measures only should be considered.

**CONCLUSIONS**

Over the last decade, C. difficile has imposed an increasingly heavy burden on the healthcare system, especially when it occurs in hospitals. The hospital-associated infection rate varies from 73% to 80% in the United States, Canada, and Europe [87–89].

A key objective should be the reduction of CDAD incidents, and, to this end, numerous scientific reviews have evaluated potential preventive measures. In this paper, fresh insight has been added with the inclusion of the expert panel’s evaluation of the relative importance of the multiple preventive measures discussed.

The suggested preventive measures that the panel group agreed upon were antibiotic stewardship, reevaluation of PPI prescription, probiotic utilization, staff education, hand hygiene, regular cleaning of patient rooms, medical equipment disinfection, rapid diagnosis and isolation of infected symptomatic patients, usage of gloves by HCPs, rapidity of implementation in CDAD outbreaks, and monitoring of surveillance data.
The panel agreed on 2 recommendations aside from those of the United States and European Infection Control guidelines: PPIs as a risk factor and probiotic utilization as a way of reducing CDAD incidence. The panel’s opinion on this last recommendation is validated by the fact that Health Canada recently approved Bio-K+ for the risk reduction of CDAD in hospital settings. The efficacy of a specific product has been confirmed by RCT, as was the case with the *L. acidophilus* CL1285 + *L. casei* LBC80R probiotic formula.

A reduction in the use of the following medications, devices, and procedures was not accepted by the panel, either because more convincing studies are needed or because the risk–benefit ratio was not logically acceptable: statins, opioid analgesics, corticosteroids, chemotherapy, hyponutrition, tube feeding, and catheter usage.

**Notes**

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**References**


49. O’Keefe SJ. Tube feeding, the microbiota, and *Clostridium difficile* infection. World J Gastroenterol 2010; 16:139–42.


76. Svensson AM, LaSala PR; Education Committee of the Academy of Clinical Laboratory Physicians and Scientists. Pathology consultation on detection of *Clostridium difficile*. Am J Clin Pathol 2012; 137:10–5.


